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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HARRIS, ALANA M

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,086	LI ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,13 and 25-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-10, 13 and 25-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 10, 2005 has been entered.

2. Claims 1, 3-10, 13 and 25-50 are pending.

Claims 1, 8-10 and 31 have been amended.

Claims 38-50 have been added.

Claim 25 has been cancelled.

Claims 1, 3-10, 13 and 25-50 are examined on the merits.

Priority

3. There continues to be insufficient proof that the proper sequences in the instant application and corresponding clones are one in the same as those listed in the priority documents. It still stands that sequences identical to SEQ ID NOS. 1-3 and 5-7 and their corresponding Figures are not found in PCT/US99/14373 (filed June 25, 1999), Provisional Applications number 60/090,906 (filed 6/25/1998) and 60/093,993 (filed July 24, 1998) and the corresponding figures. Likewise, Applicants have submitted

amendments to the Sequence Listing to reflect the correct nucleotide and amino acid sequence contained in the deposited clones, ATCC Deposit Nos. 209933, 209934 and 98809, which corresponds to SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3, respectively. The priority date afforded to claims 1, 3-10 and 25-50 is the instant application's filing date of July 13, 2001. Accordingly, since the method of claim 13 now encompasses the polynucleotides of claim 1 it is also afforded the July 13, 2001 priority date.

Maintained Objections

Specification

4. The drawings originally filed with the specification continue to be objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure.

Applicants set forth that the polynucleotides shown in corrected Figures 1A, AB-1, 1C, 2A, 2B, 2C, 2B, 2C, 3A and 3B have adequate 35 U.S.C. 112, first paragraph support in the priority documents by reference to the deposits. For the reasons set forth in the Priority section the objection is maintained.

Maintained and New Grounds of Rejection

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3-7, 13 and 25-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claim 1(e) is broadly drawn to a polynucleotide sequence that is at least 90% identical to the polynucleotide sequence that encode polypeptides, SEQ ID NOS: 5-8 and human and mouse Dnmt polypeptides. Remaining claims are broadly drawn to any part of polynucleotides that encode SEQ ID NOS: 5-8. New claims are drawn to isolated nucleic acid molecues that are at least 90% identical to SEQ ID NO: 1-4 and parts thereof. The specification while being enabling for the polynucleotides having the nucleic acid sequences of SEQ ID NOS: 1-4, does not reasonably provide enablement for variants that have at least 90% sequence identity to the polynucleotides that encode SEQ ID NOS: 5-8 and arbitrary parts of SEQ ID NO: 1-4 and polynucleotides that encode the Dnmt polypeptides. There is no guidance as to how to make these divergent sequences. The products of these 90% sequence identical molecules may encode polypeptides that possess function that may not be commensurate with the functions of the native protein. The 90% sequence identical polynucleotides may encode polypeptides that may not maintain the activities proposed in the specification. Likewise, subfragments of polynucleotides, SEQ ID NOS: 1-4 may not encode polypeptides capable of acting as enzymes which methylate unmodified CpG sites to establish tissue or gene-specific methylation patterns, such as wild type DNA cytosine

methyltransferases. It would seem that specific function(s) would be required to make the encoded protein useful for the applications disclosed in the specification, such as *in vitro* methylation at the C5 position of cytosine in DNA. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acid or acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which the protein's structure relates to its function. The specification provides essentially no guidance as to which of the infinite possible choices is likely to be successful. The true fact of the state of the art in peptide chemistry is expressed succinctly in the accompanying Lazar article (Molecular and Cellular Biology 8(3): 1247-1252, March 1988). This article presents data that substantiates the fact that the introduction of mutations in an amino acid sequence will yield products with different biological activity from the wild type protein.

From the discussion above, it is clear that the predictability of changes to the amino acid sequence is practically nil as far as biological activities are concerned. The specification fails to provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed nucleic acids in a manner reasonably correlated with the broad scope of the claims. Without such guidance, the changes which must be made in the nucleic acid sequence of SEQ ID NO: 1-4, which results in nucleic acid sequences with 90% identity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

9. The rejection claims 8 and 10 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

Applicants assert "the specification does not in *ipsis verbis* recite fragments of SEQ ID NO: 3" and "...would pose an unreasonable and restrictive burden on Applicants, see pages 16 and 17 of the Remarks. Applicants direct the Examiner's attention to page 21, lines 17-25. These points of view have been carefully considered found unpersuasive.

A "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genusbecause it would not "reasonably lead" those skilled in the art to any particular species). In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) In essence Applicants "...discose a forest in the original application, and then later pick a tree out of the forest and say 'here is my invention.", see Purdue Pharma L.D. v. Faulding Inc. 230F.39 1320, 1326, 56 USPQ2d 1481, 1486 (Fed. Cir. 2000). What Applicants assert is support for the text in claims 8 and 10 is not sufficient. Furthermore, the text pointed out by Applicants continues not to support the unambiguous contemplation of at least 50 and 100 nucleotides. The text Applicants have pointed out does not support the exclusion of polynucleotides less than 50 nucleotides and 100 nucleotides for claims 8 and 10, respectively and accordingly the rejection is maintained.

10. The rejection of claims 1, 3-10, 24-37 and newly added claims 38-50 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide

enablement commensurate with the scope of the claimed invention is maintained and made.

Applicants assert Example 4 notes a method for screening proteins for DNA cytosine methyltransferase activity is provided, see page 20 of Remarks. Applicants also argue that "it is improper for the Examiner to reject the claims 8-10 solely on the basis that the nucleotide fragments may not encode functional polypeptides", see page 21, of the Remarks. These arguments have been considered but found unpersuasive.

Applicants have not supplied information relative to the use of these claimed mutants. While the making of the claimed polynucleotides may not be burdensome implementing these variants in the proposed applications of the specification may not be valid. As Applicants submit "the artisan will obtain mutants that have a range of activities", see page 20, first paragraph of the Remarks. The claims do not limit which particular functions the mutants should exhibit or preclude what functions they should or should not be able to perform. Notwithstanding, most of the claims suggest that a polypeptide will be produced. The specification continues to not provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed nucleic acids.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. The rejection claims 1, 3-10, 25-37 and newly added claims 38-50 under 35 U.S.C. 102(b) as being anticipated by Okano et al. (Nature Genetics 19:219 and 220, July 19, 1998), as evidenced by Accession numbers AF068625, AF068626 and AF068627 (December 6, 1999) is maintained and made.

Applicants argue that claims 31-37 are directed to polynucleotide of several ATCC Deposit numbers and the instant rejection should not be applied especially since a sequence identifier is not recited within the claims. Applicants object to the rejection of claim 28 pointing out to the Examiner that the polynucleotide encoding SEQ ID NO: 8 (i.e., SEQ ID NO: 4) has not been amended and is entitled to its earliest priority date, see Remarks submitted March 10, 2005, page 22, first paragraph. Applicants continue to assert they should be afforded a priority date that would preclude Okana as prior art. These points of view have been considered but found unpersuasive.

For the reasons of record and listed in the instant Office Action the priority date afforded to claims 1, 3-10 and 25-50 is the instant application's filing date of July 13, 2001. The burden is upon Applicants to show that all of the SEQ ID numbers and their corresponding deposited clones, drawings/sequences from priority documents are one and the same. In view of this convoluted argument and sequence information it is suggested that Applicants supply sequence alignments between all the sequences, including sequences identified by SEQ ID numbers, as well as clones and drawings. Applicants continue to state a case of an earlier priority date not supported and substantiated by any scientific evidence, declarations or affidavits.

Okano discloses isolated nucleic acid molecules that are at least 99% sequence identical to Applicants' polynucleotides that encode a polypeptide comprising SEQ ID NO: 5-7, a polynucleotide sequence complementary to the said SEQ ID numbers, a nucleotide sequence complementary to a nucleotide sequence in SEQ ID NO: 1-4, at least 100 contiguous nucleotides of SEQ ID NO: 1 and 2, see attached database sheets. The Dnmt proteins were expressed using baculovirus expression vectors, see page 220, column 1, first paragraph.

13. The rejection of claims 1, 3-10, 25-37 and newly added claims 38-50 under 35 U.S.C. 102(b) as being anticipated by Xie et al. (Gene 236(1): 87-95, 1999),as evidenced by Accession number AF067972 (February 12, 2001) is maintained and made.

Applicants argue that claims 31-37 are directed to polynucleotide of several ATCC Deposit numbers and the instant rejection should not be applied especially since a sequence identifier is not recited within the claims. Applicants object to the rejection of claim 28 pointing out to the Examiner that the polynucleotide encoding SEQ ID NO: 8 (i.e., SEQ ID NO: 4) has not been amended and is entitled to its earliest priority date, see Remarks submitted March 10, 2005, page 22, first paragraph. Applicants continue to assert they should be afforded a priority date that would preclude Xie as prior art. These points of view have been considered but found unpersuasive.

For the reasons of record and listed in the instant Office Action the priority date afforded to claims 1, 3-10 and 25-50 is the instant application's filing date of July 13,

2001. The burden is upon Applicants to show that all of the SEQ ID numbers and their corresponding deposited clones, drawings/sequences from priority documents are one and the same. In view of this convoluted argument and sequence information it is suggested that Applicants supply sequence alignments between all the sequences, including sequences identified by SEQ ID numbers, as well as clones and drawings. Applicants continue to state a case of an earlier priority date not supported and substantiated by any scientific evidence, declarations or affidavits.

Xie discloses isolated nucleic acid molecules that are at least 96% sequence identical to Applicants' polynucleotides that encode a polypeptide comprising SEQ ID NO: 5, 7, 8, a polynucleotide sequence complementary to the said SEQ ID numbers, a nucleotide sequence complementary to a nucleotide sequence in SEQ ID NO: 1-4, at least 100 contiguous nucleotides of SEQ ID NO: 1-4, see attached database sheets. The Dnmt proteins were expressed using baculovirus expression vectors, see page 220, column 1, first paragraph.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1, 3-10, 13, 25-37 and newly added claims 38-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Okano et al. (Nature Genetics 19:219 and

220, July 19, 1998), as evidenced by Accession numbers AF068625, AF068626 and AF068627 (December 6, 1999), and in view of U.S. Patent 6,492,168 BI (April 22, 1998).

The teachings of Okano have been presented in the 102(b) rejections. Okano does not teach a method for *in vitro de novo* methylation of DNA comprising the limitations listed in sections a-c of the claim. However, the patent teaches a nucleic acid sequence that is complementary to any one of SEQ ID NO: 5-8, which is capable of contacting DNA allowing for a method utilizing an expressed novel methyltransferase (M.CviPI) to methylate GpC in vitro, see column 18, line s31-43 and column 20, lines 60-67. In a reaction mixture containing buffered solutions, cofactors, a DNA substrate and M.CviPI the *in vitro de novo* methylation DNA assay was conducted. The DNA was purified from the reaction with ethanol precipitation. It would have been prima facie obvious to one of ordinary skill in the art at the time of the claimed invention to implement a well established and art know method. One of ordinary skill in the art would have been motivated to do so at the time of the claimed invention based on the teachings of both references.

16. Claims 1, 3-10, 13, 25-37 and newly added claims 38-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xie et al. (Gene 236(1): 87-95, 1999),as evidenced by Accession number AF067972 (February 12, 2001), and in view of U.S. Patent 6,492,168 BI (April 22, 1998).

The teachings of Xie have been presented in the 102(b) rejections. Xie does not teach a method for *in vitro de novo* methylation of DNA comprising the limitations listed in sections a-c of the claim. However, the patent teaches a nucleic acid sequence that is complementary to any one of SEQ ID NO: 5-8, which is capable of contacting DNA allowing for a method utilizing an expressed novel methyltransferase (M.CviPI) to methylate GpC in vitro, see column 18, line s31-43 and column 20, lines 60-67. In a reaction mixture containing buffered solutions, cofactors, a DNA substrate and M.CviPI the *in vitro de novo* methylation DNA assay was conducted. The DNA was purified from the reaction with ethanol precipitation. It would have been prima facie obvious to one of ordinary skill in the art at the time of the claimed invention to implement a well established and art know method. One of ordinary skill in the art would have been motivated to do so at the time of the claimed invention based on the teachings of both references.

Double Patenting

17. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

18. Claims 1, 3-10, 13 and 25-50 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-10, 13, 24-37 and 51-55 of copending

Application No. 10/623,813 (filed July 22, 2003). This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The examiner works a flexible schedule, however she can normally be reached between the hours of 6:30 am to 5:30 pm with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
31 May 2005